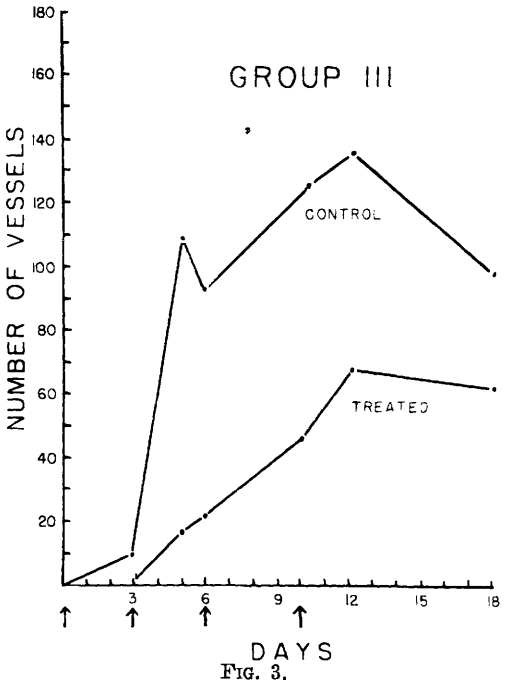

FIG. 3.
Same as Fig. 1, except that 0.5N NaOH was used.

trol eyes showed all the vessels to be superficial, and revealed no gross difference in caliber or branching.

Discussion. The experiments reported here appear to demonstrate the depression of capillary growth by the local application of cortisone. The mechanism of this action is unknown. Two possible mechanisms suggest themselves as the mode of action of cortisone: (1) the blocking of the chemotactic influence on the limbus capillaries exerted by the injured corneal tissue, and (2) the prevention of the response of the endothelial cells to a chemotactic stimulus by inhibition of processes essential for capillary proliferation. Vascularization of the cornea has been suggested to be initiated by the enzymatic hydrolysis of the mucopolysaccharide of the ground substance of the cornea(5). Cortisone has been claimed to be an inhibitor of the action of hyaluronidase both on dermal spreading in animals(6) and in man(7) and on the permeability of the synovial membrane(8). Corneal vascularization appears to be especially suited to submit these hypotheses to experimental proof.

Summary. The subconjunctival injection of cortisone inhibits markedly the vascularization of the cornea caused by intracorneal injection of alkali.

5. Meyer, K., in Modern Trends in Ophthalmology II, New York and London, 1947.

6. Opsahl, J., *Yale J. Biol. and Med.*, 1949, v22, 115.

7. Shuman, C. R., and Finestone, A. J., PROC. SOC. EXP. BIOL. AND MED., 1950, v73, 248.

8. Seifter, J., Baeder, D. H., and Begany, A. J., PROC. SOC. EXP. BIOL. AND MED., 1949, v72, 277.

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Antihistamine Therapy in Experimental Shock.* (17823)

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Among the theories proposed to explain the cause of secondary shock there have been many suggestions that histamine, "H substance" and similar agents, released by injured tissue, account for the shock symptoms. Repeated injections of histamine have been reported by Dale and Laidlaw(1) to induce fluid loss and cardiovascular changes typical of secondary shock. In shock from burns and occlusion tourniquets loss of fluid from the blood has been considered an important contributing factor to cardiovascular failure. The possibility that such fluid shifts might be reduced by the use of antihistamine

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1. Dale, H. H., and Laidlaw, P. P., *J. Physiol.*, 1919, v52, 355.

TABLE I.
Tourniquet Shock Mortality in Treated and Control Rats.

Treatment	No. of animals	% mortality 24 hr	Temp. °C
Benadryl, 20 mg/kg	62	90	28.5-32.5
Controls—Saline	83	76	" "
Thephorin, 25 mg/kg	72	58	
Controls—Saline	76	41	24-28
Thephorin, 50 mg/kg	71	93	"
Controls—Saline	67	66	"

drugs has suggested itself to several experimenters. Halpern(2) reported that passage of dye from the peritoneal cavity was reduced, and pumonary edema from epinephrine administration was prevented by dimethylamino - 2 - propyl - L - phenolthiazine (Phenergan). Lowy and Code(3) applied antihistaminics locally in man and found no influence on flares produced by small skin burns, but found flares induced by local freezing could be inhibited by the drugs. Jourdan and Chatonnet(4) found no beneficial results when shock induced by muscle trauma was treated with N-dimethylamino ethyl-N-benzylaniline (Antergan). In view of these conflicting reports, a series of experiments were undertaken to test the effects of antihistaminics on survival and fluid loss in experimental shock.

Methods. Rats anesthetized with 32.5 mg/kg sodium pentobarbital were shocked by application of rubber bands to the hind legs for 3 hours and 40 minutes. According to Shipley, Meyer and McShan(5) this procedure results in 47% mortality, but our rate (41-76%) was somewhat higher, which we have ascribed to the high room temperatures prevailing during the summer when much of the work was done. Two antihistaminics were used, Beta-dimethylaminoethylbenzhydryl ether hydrochloride (Benadryl)† and 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (Thephorin)‡. Benadryl was given intraperitoneally 20 mg/kg in one dose about 15 minutes before release of the tourniquet, or in two doses, with the second about 4 hours after release. Thephorin was given in doses of 25 or 50 mg/kg, either as a single intraperitoneal injection, or in 2 doses, the first given about 15 minutes before application, and the second before release of the tourniquets.

Dogs deeply anesthetized with the dose of pentobarbital given above, plus 5 mg/kg morphine sulfate, were shocked by exposing the hind quarters to water at 90°C for 5 seconds(6). Before shock, 20 mg/kg Benadryl i.m. was given, followed after shocking by 5 mg/kg every 3 hours for 24 hours. In a second series, the shock therapy consisted of 40 mg% Benadryl in saline administered intravenously at a rate of 100 cc/kg/24 hours. Control animals were given saline instead of the drug in both groups. Hematocrit readings, and blood and serum specific gravity determinations by the copper sulfate method were made before shock, and at 3-hour intervals thereafter. Blood pressure was recorded from the carotid artery by a mercury manometer.

Results. The 24-hour mortality rate for rats shown in Table I indicates that neither of the 2 antihistaminics used were of benefit in tourniquet shock. Large doses, in fact, decreased survival noticeably.

Table II summarizes the results of burn shock treatment in dogs. No marked decrease in mortality resulted from Benadryl

2. Halpern, B. N., *Am. J. Physiol.*, 1948, v155, 442.

3. Lowy, A., and Code, C. F., *Am. J. Physiol.*, 1948, v155, 452.

4. Jourdan, F., and Chatonnet, J., *Compt. rend. Soc. de biol.*, 1943, v137, 559.

5. Shipley, E. G., Meyer, R. K., and McShan, W. H., PROC. SOC. EXP. BIOL. AND MED., 1945, v60, 340.

† Supplied by Parke, Davis and Co., Detroit, Mich.

‡ Supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.

6. Elman, R., and Brown, F. C., *War Med.*, 1943, v3, 477.

TABLE II.
Burn Shock Mortality in Treated and Control Dogs.

Treatment	No. of animals	% mortality 24 hr	Avg hr survival
Benadryl i.m.	28	89	11.5
Controls—Saline i.m.	26	85	12.9
Benadryl + saline i.v.	11	64	19.4
Control—Saline i.v.	11	73	14.4

therapy, although there may be some suggestion that saline infusion plus this drug aided survival. Hematocrit, and blood and serum specific gravity changes did not vary consistently between treated and control groups. Blood pressure readings in the treated group tended to be slightly above those of the controls throughout the survival period, but this did not appear to be of significant magnitude.

Discussion. The results above indicate that the 2 antihistaminics used were without benefit, or somewhat detrimental, to animals in burn and tourniquet shock. Page and Green(7) found that large doses of Benadryl caused vascular refractoriness in the dog, with the result that larger than normal amounts of saline could be infused into the animal. This was ascribed to increased capacity of the vascular bed, or to increased permeability of the capillaries. Our results in the shocked dog do not suggest this, since the changes in blood pressure and hemoconcentration were not consistently different in the control and treated animals. Possibly the larger doses of Benadryl used by Page and Green account for the refractory state of the vascular bed in their animals.

Summary. The administration of Benadryl or Thephorin to rats subjected to tourniquet shock tended to increase mortality if given in relatively large doses. Dogs in burn shock treated with Benadryl did not differ significantly from untreated controls with respect to mortality, blood pressure, hematocrit, and blood and serum specific gravity.

7. Page, I., and Green, A., *Am. J. Physiol.*, 1949, v156, 405.

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A Rapid Method for Determination of the Aureomycin Concentration of the Blood. (17824)

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The need for a speedy report of the blood concentration is particularly urgent with aureomycin therapy. Nausea, vomiting and diarrhea are not uncommon with this drug, and it is often difficult to decide whether or not the administered drug has been adsorbed and to what extent. This need is further emphasized by the increasing use of such adjuvants as aluminum hydroxide gels to counteract the toxic symptoms. Waisbren and Hueckel(1) have shown that when aluminum hydroxide gel is administered with aureomycin, a lowered level of aureomycin in the blood results. A method of assay which can be completed and reported within 5 hours after the specimen is received in the laboratory, no matter what time of day or night, is the subject of this report. The procedure is a tube dilution method, employing *Proteus vulgaris* OX-19 as the standard organism and a special urea-phenol red broth as the medium. The principle of the test is based upon the bacteriostatic action of the antibiotic on the test strain and the inhibition of the rapid

1. Waisbren, B. A., and Hueckel, J. S., PROC. SOC. EXP. BIOL. AND MED., 1950, v73, 73.